Metabolic and Organelle Morphology Defects in Mice and Human Patients Define Spinocerebellar Ataxia Type 7 as a Mitochondrial Disease.

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Public Summary:
This publication uses a mouse and human models to gain insights on spinocerebellar ataxia. We found that this disorder has an unknown mitochondrial dysfunction that could explain some of the clinical symptoms and opens novel therapeutic opportunities.

Scientific Abstract:
Spinocerebellar ataxia type 7 (SCA7) is a retinal-cerebellar degenerative disorder caused by CAG-polyglutamine (polyQ) repeat expansions in the ataxin-7 gene. As many SCA7 clinical phenotypes occur in mitochondrial disorders, and magnetic resonance spectroscopy of patients revealed altered energy metabolism, we considered a role for mitochondrial dysfunction. Studies of SCA7 mice uncovered marked impairments in oxygen consumption and respiratory exchange. When we examined cerebellar Purkinje cells in mice, we observed mitochondrial network abnormalities, with enlarged mitochondria upon ultrastructural analysis. We developed stem cell models from patients and created stem cell knockout rescue systems, documenting mitochondrial morphology defects, impaired oxidative metabolism, and reduced expression of nicotinamide adenine dinucleotide (NAD(+)) production enzymes in SCA7 models. We observed NAD(+) reductions in mitochondria of SCA7 patient NPCs using ratiometric fluorescent sensors and documented alterations in tryptophan-kynurenine metabolism in patients. Our results indicate that mitochondrial dysfunction, stemming from decreased NAD(+), is a defining feature of SCA7.